

C1  
SCF is expressed as membrane-associated forms of either 248 or 220 amino acid residues (Galli et al., 1994, Lev et al., 1994, Besmer et al., 1997, Broudy, 1997). The two forms are a consequence of alternative mRNA splicing that includes or excludes exon 6. Exon 6 encodes a proteolytic cleavage site such that soluble SCF<sup>1-165</sup> is released from the 248 amino-acid precursor. Residues 166-189 represent a tether to the membrane, residues 190-221 represent a hydrophobic transmembrane segment, and residues 222-248 represent a cytoplasmic domain. The 220 amino acid residue form lacks the cleavage site and tends to remain membrane-bound. Soluble SCF exists as a non-covalently associated dimer (Arakawa et al., 1991). Each SCF monomer contains two intra-chain disulfide bridges, Cys4-Cys 89 and Cys43-Cys138 (Langley et al, 1992). The N-terminal 141 residues of SCF have been identified as a functional core, SCF<sup>1-141</sup> (SEQ ID NO:1), that includes the dimer interface and portions that bind and activate the receptor Kit (Langley et al., 1994).

---

Please replace the paragraph beginning page 10, line 3, with the following rewritten paragraph:

---

This invention provides a method for designing a compound (drug) capable of binding to the receptor of stem cell factor (SCF), Kit, comprising the steps of: a) determining a receptor binding site on the SCF based on the three dimensional structure of SCF (SEQ ID NO:1) or an SCF polypeptide capable of binding the receptor; and b) designing a compound comprising an entity that binds the SCF receptor. Accordingly, the designed compound is an SCF ligand analog, since a portion or part of the compound, "the entity", mimics the portion of SCF that binds to the SCF receptor, Kit. In step (a), and infra, the receptor binding site may be determined

Applicant: Wayne A. Hendrickson et al  
U.S. Serial No.: 09/609,027  
Filed: June 29, 2000  
Page 3

from atomic coordinates computed from X-ray diffraction data of a crystal comprising a polypeptide having an amino acid sequence portion of SCF capable of binding the receptor.

---

Please replace the paragraph beginning page 10, line 19, with the following rewritten paragraph:

---

C2  
This invention provides a compound designed by the above-described method for designing a compound capable of binding to the receptor site of stem cell factor (SCF), Kit, comprising the steps of: a) determining a receptor binding site, on the SCF (SEQ ID NO;1) based on the atomic coordinates computed from X-ray diffraction data of a crystal comprising a polypeptide having an amino acid sequence portion of SCF capable of binding a ligand; and b) designing a compound comprising an entity that binds the SCF receptor. As used herein, the entity, i.e. the portion, of the designed compound fits the ligand binding site on the SCF receptor.

---

Please replace the paragraph beginning page 11, line 11, with the following rewritten paragraph:

---

C3  
This invention provides an isolated stem cell factor (SCF) molecule, which is an altered SCF, comprising any portion of amino acids 1-165 of a human SCF polypeptide (SEQ ID NO;22), optionally comprising an N-terminal methionine before amino acid residue 1, wherein the polypeptide has an amino acid sequence portion of SCF capable of binding to the SCF receptor, Kit. Amino acid residue 1 of SCF is E, glutamic acid.

---

Please replace the paragraph beginning page 20, line 11, with the following rewritten paragraph:

C4  
Based on the correlation of structure to biological activity, one aspect of the present invention relates to SCF analogs. These analogs are molecules which have more, fewer, different or modified amino acid residues from the SCF amino acid sequence. The modifications may be by addition, substitution, or deletion of one or more amino acid residues. The modification may include the addition or substitution of analogs of the amino acids themselves, such as peptidomimetics or amino acids with altered moieties such as altered side groups. The SCF used as a basis for comparison may be of human, animal or recombinant nucleic acid-technology origin (although the working examples disclosed herein are based on the recombinant production of the 141 amino acid species of human SCF (SEQ ID NO;1), optionally having an extra N-terminal methionine residue). The analogs may possess functions different from natural human SCF molecule, or may exhibit the same functions, or varying degrees of the same functions. For example, the analogs may be designed to have a higher or lower biological activity, have a longer shelf-life or a decrease in stability, be easier to formulate, or more difficult to combine with other ingredients. The analogs may bind receptor but elicit no biological activity and may therefore be useful as an antagonist against SCF effect (as, for example, in the overproduction of SCF). From time to time herein the present analogs are referred to as proteins or peptides for convenience, but contemplated herein are other types of molecules, such as peptidomimetics or chemically modified peptides.

---

Please replace the paragraph beginning page 33, line 3, with the following rewritten paragraph:

---

C5  
In an embodiment of the above-described method the computer

C5  
Cont'd

expression allows for display of the amino acids of the SCF molecule. In another embodiment of the method the computer expression allows for display of each atom of the SCF molecule. In a further embodiment of the method the SCF molecule is a native or a selenomethionyl SCF. In another embodiment of the method the site on the SCF molecule for alteration is a receptor binding site on the surface of the SCF molecule. In a further embodiment of the method the receptor binding site comprises amino acid residues 79-85 (of SEQ ID NO:1). The SCF molecule may be a recombinant human SCF or a wild type naturally occurring human SCF. SCF wild type and recombinant may also be of other sources such as but not limited to rat or mouse. In an embodiment of the above-described method, the atomic coordinates of the crystal structure are set forth in Figure 8. In another embodiment the SCF analog comprises a polypeptide having an amino acid sequence portion of SCF capable of binding a receptor and having the overall three-dimensional conformation as shown in Figures 2A-2B, wherein the three-dimensional conformation is: a) anti-parallel, double-cross over 4-alpha helical bundle with a left hand twist; and b) overall dimensions of approximately 85 Å x 30 Å x 20 Å. In an embodiment the SCF analog comprises electron density distributions as set forth in Figures 1A, 1B, and 1C. In a further embodiment the SCF molecule is a native SCF or a selenomethionyl SCF.

---

Please replace the paragraph beginning page 34, line 9, with the following rewritten paragraph:

---

C6

In another embodiment the receptor binding site comprises approximately amino acid residues 79-95 (of SEQ ID NO:1).

---

Applicant: Wayne A. Hendrickson et al  
U.S. Serial No.: 09/609,027  
Filed: June 29, 2000  
Page 6

Please replace the paragraph beginning page 34, line 29, with the following rewritten paragraph:

---

c7  
This invention provides a composition comprising an isolated SCF analog prepared according to the above-described method effective to treat a subject and a pharmaceutically acceptable carrier. In an embodiment of the composition, the isolated SCF analog has an alteration in at least one atom of the atomic coordinates of the crystal structure set forth in Figure 8. In another embodiment the isolated SCF analog comprises a polypeptide having an amino acid sequence portion of SCF capable of binding a receptor and having the overall three-dimensional conformation as shown in Figures 2A-2B, or an alteration thereof, wherein the three-dimensional conformation is: a) anti-parallel, double-cross over 4-alpha helical bundle with a left hand twist; and b) overall dimensions of approximately 85 Å x 30 Å x 20 Å. In a further embodiment the isolated SCF analog comprises electron density distributions as set forth in Figures 1A, 1B, and 1C. In an embodiment the isolated SCF analog comprises a native SCF1-165 (SEQ ID NO:22), a recombinant seleno-methionyl SCF1-141 (of SEQ ID NO:1), or a recombinant selenomethionyl SCF1-165 (of SEQ ID NO:22).

---

Please replace the paragraph beginning page 35, line 24, with the following rewritten paragraph:

---

c8  
In an embodiment of the composition the site on the isolated SCF molecule for alteration is a receptor binding site on the surface of the SCF molecule. In a further embodiment the receptor binding site comprises approximately amino acid residues 79-95 of SEQ ID NO:1.

---

Applicant: Wayne A. Hendrickson et al  
U.S. Serial No.: 09/609,027  
Filed: June 29, 2000  
Page 7

Please replace the paragraph beginning page 35, line 30, with the following rewritten paragraph:

---

C9  
This invention provides a method of treating a subject having a disorder requiring SCF comprising administration of a composition comprising an isolated SCF analog prepared by the method of preparing a SCF analog or a compound designed by the method of designing a compound capable of binding to the SCF receptor as described infra. In an embodiment the subject has a blood disorder. In another embodiment the disorder which the subject has is anemia, myeloproliferative disorder, neoplasia, nerve damage, infertility, intestinal damage, a pigmentation disorder, or immunodeficiency. In an embodiment the administration of the isolated SCF analog is for ex vivo or in vitro production of peripheral blood progenitors, ex vivo or in vitro stem cell expansion, ex vivo or in vitro growth of epithelial cells, ex vivo or in vitro growth of stromal cells, ex vivo or in vitro dendritic cell stimulation, and in vivo cell mobilization. In an embodiment the isolated SCF analog is administered orally or by any other routes described infra. In an embodiment the isolated SCF analog has an alteration in at least one atom of the atomic coordinates of the crystal structure set forth in Figure 8. In a further embodiment the isolated SCF analog comprises a native SCF1-165 (SEQ ID NO:22) or a recombinant selenomethionyl SCF1-141 (of SEQ ID NO:1). In another embodiment the site on the isolated SCF molecule for alteration is a receptor binding site on the surface of the SCF molecule. In a further embodiment the receptor binding site comprises approximately amino acid residues 79-95. In an embodiment the isolated SCF analog comprises a native or recombinant SCF1-165 (SEQ ID NO:22 or a recombinant selenomethionyl SCF1-141 (of SEQ ID NO:1). As used herein throughout SCF receptor is Kit.

---

Applicant: Wayne A. Hendrickson et al  
U.S. Serial No.: 09/609,027  
Filed: June 29, 2000  
Page 8

Please replace the paragraph beginning page 38, line 1, with the following rewritten paragraph:

C10  
In an embodiment, the oligopeptide comprises a sequence, wherein functional moiety  $F_1$  corresponds to a segment of amino acid residues from within N-terminal residues 1-10 of SCF, functional moiety  $F_2$  corresponds to a segment of amino acid residues from within residues 79-95 of SCF (SEQ ID NO:1), and functional moiety  $F_3$  corresponds to a segment of amino acid residues located within three amino acid residues of amino acid residue 127, wherein  $F_1$ ,  $F_2$ , and  $F_3$  are connected by connecting peptide segments  $X_n$ ,  $X_m$ , and  $X_p$ , respectively, wherein  $n=0-5$ ,  $m=0-5$  and  $p=3-8$  amino acid residues, respectively, and the conjugation moiety  $F_L$  is a cysteine residue.

Please replace the paragraph beginning page 38, line 19, with the following rewritten paragraph:

C11  
The amino acid residues located within 3 amino acid residues of amino acid residue 127 (SEQ ID NO:1) may be located within 3 residues in either direction of residue 127. In further embodiments the amino acid residues may be from 4 to 10 amino acid residues in either direction of amino acid residue 127.

Please replace the paragraph beginning page 40, line 1, with the following rewritten paragraph:

C12  
In another embodiment the oligopeptide comprises a sequence, wherein functional moiety  $F_1$  corresponds to a segment of amino acid residues from within N-terminal residues 1-10 of SCF (SEQ ID NO:1), functional moiety  $F_2$  corresponds to a segment of amino acid residues from within residues 79-95 of SCF, and functional moiety

C12  
Cont'd

F<sub>3</sub> corresponds to a segment of amino acid residues located within three amino acid residues of amino acid residue 127, wherein F<sub>1</sub>, F<sub>2</sub>, and F<sub>3</sub> are connected by connecting peptide segments X<sub>n</sub>, X<sub>m</sub>, and X<sub>p</sub>, respectively, wherein n=0-5, m=0-5 and p=3-8 amino acid residues, respectively, and the conjugation moiety F<sub>L</sub> is a cysteine residue. In a further embodiment the functional moieties F<sub>1</sub>, F<sub>2</sub>, and F<sub>3</sub> on the ligand heads have been selected by bacterial phage display for optimal receptor binding. In an embodiment the functional moieties and connecting peptide segments of an active oligopeptide ligand head are replaced by chemical mimetics. In another embodiment an appropriate chemical scaffold of connecting segments has been designed to comprise (present) functional moieties F<sub>1</sub>, F<sub>2</sub>, and F<sub>3</sub>, which have been selected by combinatorial chemistry for optimal receptor binding from a library of chemical moieties complementary to receptor-binding sites on the surface of SCF. In another embodiment the linker comprises an organic polymer having two ends capped at each end by a reactive capping moiety, F<sub>c</sub>, which react covalently with the conjugation moiety, F<sub>L</sub>, on the ligand head. In a further embodiment the organic polymer is polyethyleneglycol (PEG) comprising the structure H[OCH<sub>2</sub>CH<sub>2</sub>]<sub>n</sub>OH, wherein n is 10-20. In another embodiment the capping moiety, F<sub>c</sub>, is a thiol-reactive group such as N-ethyl maleimide. In an embodiment the conjugating moiety, F<sub>L</sub>, is a thiol containing group such as cysteine.

---

Please replace the paragraph beginning page 41, line 4, with the following rewritten paragraph:

---

C13

This invention provides a method of treating a subject comprising administration of a compound designed by the above described method. In an embodiment the subject has a blood disorder. In a further embodiment the blood disorder is anemia or

C13  
Cont'd

immunodeficiency. In an embodiment the compound is administered orally or any other routes. In an embodiment the compound is an isolated SCF analog. In another embodiment the compound comprises an isolated SCF analog, whose alteration site is a receptor binding site on the surface of the altered SCF molecule. In another embodiment of the method the composition comprises a double-headed receptor SCF ligand analog having the structure set forth in Figure 10A. In an embodiment each ligand head of the double-headed SCF ligand analog is an oligopeptide having the structure set forth in Figure 10B. In another embodiment the oligopeptide comprises a sequence, wherein functional moiety  $F_1$  corresponds to a segment of amino acid residues from within N-terminal residues 1-10 of SCF, functional moiety  $F_2$  corresponds to a segment of amino acid residues from within residues 79-95 of SCF, and functional moiety  $F_3$  corresponds to a segment of amino acid residues located within three amino acid residues of amino acid residue 127, wherein  $F_1$ ,  $F_2$ , and  $F_3$  are connected by connecting peptide segments  $X_n$ ,  $X_m$ , and  $X_p$ , respectively, wherein  $n=0-5$ ,  $m=0-5$  and  $p=3-8$  amino acid residues, respectively, and the conjugation moiety  $F_c$  is a cysteine residue. In a further embodiment the functional moieties  $F_1$ ,  $F_2$ , and  $F_3$  on the ligand heads have been selected by bacterial phage display for optimal receptor binding. In an embodiment the functional moieties and connecting peptide segments of an active oligopeptide ligand head are replaced by chemical mimetics. In another embodiment an appropriate chemical scaffold of connecting segments has been designed to comprise (present) functional moieties  $F_1$ ,  $F_2$ , and  $F_3$ , which have been selected by combinatorial chemistry for optimal receptor binding from a library of chemical moieties complementary to receptor-binding sites on the surface of SCF. In another embodiment the linker comprises an organic polymer having two ends capped at each end by a reactive capping moiety,  $F_c$ , which react

C13  
Corrected

covalently with the conjugation moiety,  $F_L$ , on the ligand head. In a further embodiment the organic polymer is polyethyleneglycol (PEG) comprising the structure  $H[OCH_2CH_2]_nOH$ , wherein  $n$  is 10-20. In another embodiment the capping moiety,  $F_c$ , is a thiol-reactive group such as N-ethyl maleimide. In an embodiment the conjugating moiety,  $F_L$ , is a thiol containing group such as cysteine.

---

Please replace the paragraph beginning page 44, line 20, with the following rewritten paragraph:

---

C14

This invention provides an isolated stem cell factor (SCF) molecule, which is an altered SCF, comprising any portion of amino acids 1-165 of a human SCF polypeptide (SEQ ID NO:7), optionally comprising an N-terminal methionine before amino acid residue 1, wherein the polypeptide has an amino acid sequence portion of SCF capable of binding to the SCF receptor. In an embodiment of the altered isolated stem cell factor molecule an alteration is selected from the group consisting of deletion, insertion and substitution of at least one amino acid residue from the naturally occurring amino acid sequence of SCF.

---

Please replace the paragraph beginning page 45, line 1, with the following rewritten paragraph:

---

C15

In a further embodiment an alteration is a truncated SCF comprising amino acids 1-141 of a human SCF polypeptide (SEQ ID NO:1), optionally comprising an N-terminal methionine before amino acid residue 1, E. In another embodiment the three-dimensional structure is altered from the atomic coordinates are set forth in Figure 8. In yet another embodiment the electron density distribution map is altered from the atomic coordinates are set forth in Figures 1A,

Applicant: Wayne A. Hendrickson et al  
U.S. Serial No.: 09/609,027  
Filed: June 29, 2000  
Page 12

C15  
cont'd

1B, or 1C. In a still further embodiment the substitution of at least one amino acid residue is selected from the group consisting of SCF(Y26C) (SEQ ID NO:11) disulfide-linked dimer, SCF(D25C) (SEQ ID NO:12), SCF(K62C) (SEQ ID NO:13), SCF(K78N, (SEQ ID NO:14); N81K (SEQ ID NO:15)), SCF(R117A, (SEQ ID NO:16); I118A (SEQ ID NO:17)), SCF(E92, (SEQ ID NO:18); S95A (SEQ ID NO:19)), and SCF(D124A, (SEQ ID NO:21); K127D (SEQ ID NO:22)). In another embodiment the overall three-dimensional conformation of the stem cell factor molecule has an altered three-dimensional structure of the  $\alpha$ C- $\beta$ 2 loop.

---

Please replace the paragraph beginning page 45, line 19, with the following rewritten paragraph:

---

C16

This invention provides a pharmaceutical composition comprising the above described altered isolated SCF molecule and a pharmaceutically acceptable carrier. In an embodiment the altered SCF molecule molecule is a hybrid molecule of the altered stem cell factor molecule and a second protein or fragment thereof. As used herein, an SCF hybrid molecule is defined as a molecule wherein analog SCF is combined with with part or all of another protein such as another cytokine or another protein, which for example, effects signal transduction via entry through the cell through a SCF-SCF receptor transport mechanism. In an embodiment the alteration of the  $\alpha$ C- $\beta$ 2 loop is a change in length of the amino acid sequence of the  $\alpha$ C- $\beta$ 2 loop by a deletion or an insertion of at least one amino acid residue or a change in at least one amino acid residue from the naturally occurring amino acid residue(s) of the  $\alpha$ C- $\beta$ 2 loop. In another embodiment the change in said at least one amino acid residue from the naturally occurring amino acid residue(s) is selected from the group consisting of SCF(Y26C) (SEQ ID NO:11) disulfide-linked dimer, SCF(D25C) (SEQ ID NO:12),

Applicant: Wayne A. Hendrickson et al  
U.S. Serial No.: 09/609,027  
Filed: June 29, 2000  
Page 13

SCF(K62C) (SEQ ID NO:13), SCF(K78N, (SEQ ID NO:14); N81K (SEQ ID NO:15)), SCF(R117A, (SEQ ID NO:16); I118A (SEQ ID NO:17)), SCF(E92A, (SEQ ID NO:18); S95A (SEQ ID NO:19)), and SCF(D124A, (SEQ ID NO:21); K127D (SEQ ID NO:22)).

Please replace the paragraph beginning page 47, line 7, with the following rewritten paragraph:

C17  
Human SCF<sup>1-141</sup> (SEQ ID NO:1) was expressed recombinantly in *E. coli* as described previously (Langley et al., 1994). For expression of SeMet SCF<sup>1-141</sup>, the expression vector was transfected into the methionine auxotrophic *E. coli* strain FM5. Fermentation was carried out at 30°C in 8 liters of minimal medium consisting of ammonium sulfate (10 g/liter), glucose (5 g/liter), methionine (0.125 g/liter), phosphate salts, magnesium, citric acid, trace metals, and vitamins. When an OD<sub>600</sub> of 3-5 was reached, a feed medium was added that consisted of the following components in a total volume of 1 liter: 100 g of ammonium sulfate, 450 g of glucose, 2 g of methionine, magnesium, trace metals, and vitamins. At an OD<sub>600</sub> of 12.4, induction medium (one liter containing 100 g of ammonium sulfate, 300 g of glucose, and 1 g of selenomethionine) was added and fermentation proceeded at 30°C. Five hours later (at an OD<sub>600</sub> of approximately 16), the temperature was raised to 42°C to induce SCF expression and additional selenomethionine (1 g) was added. Cells were harvested 4 hours after the temperature shift (OD<sub>600</sub> of approximately 16). SeMet SCF<sup>1-141</sup> expression was estimated as 0.5 g/liter. Both SCF<sup>1-141</sup> and SeMetSCF<sup>1-141</sup> were purified with minor modifications to previously described procedures (Langley et al., 1992, 1994). Both retain the initiating methionine (or SeMet) residue [position (-1)] (Langley et al., 1994). N-terminal amino acid sequencing was performed as described (Lu et al., 1991). About

Applicant: Wayne A. Hendrickson et al  
U.S. Serial No.: 09/609,027  
Filed: June 29, 2000  
Page 14

C17  
Cont'd

90% SeMet was present in SeMetSCF<sup>1-141</sup> at each of the Met positions, based on amino acid analysis and N-terminal sequencing results (i.e. lack of recovery of Met residues for SeMetSCF<sup>1-141</sup> in comparison with SCF<sup>1-141</sup>; data not shown).

---

Please replace the paragraph beginning page 68, line 20, with the following rewritten paragraph:

---

C18

From studies of truncation and point mutants, Langley et al (1994) demonstrated that the N-terminal residues 1-4 and 1-10 and the Cys4-Cys89 disulfide bond are required for receptor binding and bioactivity, and that the Cys43-Cys138 disulfide bond and C-terminal residues past 127 are not required for receptor binding but may have some roles in cell proliferation activity. Moreover, alterations at Asn10 and Asn11 brought about by chemical isomerization or by mutagenesis have positive or negative effects depending on the substitution (Hsu et al., 1998). A quadruple mutant of SCF (Arg121Asn, Asp124Asn, Lys127Asp and Asp128Lys) was found to be defective in bioactivity (Matous et al., 1996). The molecular cause of this deficiency may be specific to Lys127 or due to indirect electrostatic effects. Arg121 and Asp124 are adjacent to the main N-linked glycosylation site, which is not involved in binding (see infra), and Asp128 is absent in the 1-127 truncation mutant (SEQ ID NO:4) that retains full receptor-binding activity (Langley et al., 1994). Moreover, a study of human-murine SCF chimeras narrowed the important receptor recognition epitopes to within residues 1 to 35 and 79 to 97 (Matous et al., 1996), and the epitope of a neutralizing antibody was mapped to the region of residues 60-95 (Mendiaz et al., 1996) and 79-97 (Matous et al., 1996).

---

Applicant: Wayne A. Hendrickson et al  
U.S. Serial No.: 09/609,027  
Filed: June 29, 2000  
Page 15

Please replace the paragraph beginning page 77, line 3, with the following rewritten paragraph:

C19  
Based on the X-ray crystallographic structure of SCF, several analogs were made and their biological activities were measured and compared to that of SCF wild type.

<u>Analogs</u>	<u>Biological Activity</u> (Approximate, compared to wild type SCF)
SCF(Y26C) disulfide linker (SEQ ID NO:11)	2 to 3 fold higher
SCF(D25C) (SEQ ID NO:12)	100 fold lower
SCF(K62C) (SEQ ID NO:13)	7 fold lower

These analogs were designed based on the structure of the dimer interface of SCF, which is a non-covalent dimer. Leu22, Pro23, Lys24, Asp25, Tyr26, Lys62 and Phe63 are in the dimer surface. The side chains of Leu22, Pro23, Tyr26, and Phe63 reside in the buried center of the dimerization site and are involved in hydrophobic interactions. The hydrophilic side chains of Lys24, Asp25 and Lys62 from each monomer residue in the solvent accessible surface, and are involved in ionic interactions. By replacing Tyr26 with Cys, [SCF(Y26C)], it was anticipated that a dimer covalently linked by a disulfide bond between the C26 residue of each monomer would form because the distance between the  $\beta$  carbons of the two Cys26 residues would be less than 3Å.

<u>Analogs</u>	<u>Biological Activity</u> (Approximate, compared to wild type SCF)
----------------	---

Applicant: Wayne A. Hendrickson et al  
U.S. Serial No.: 09/609,027  
Filed: June 29, 2000  
Page 16

C19  
Cont'd

SCF(K78N, N81K) 3 fold lower  
(SEQ ID NO:14 & SEQ ID NO:15)

SCF(R117A, I118A) 10 fold lower  
(SEQ ID NO:16 & SEQ ID NO:17)

SCF(E92A, S95A) no change  
(SEQ ID NO:19 & SEQ ID NO:20)

SCF(D124A, K127D) no change  
(SEQ ID NO:21 & SEQ ID NO:22)

These analogs were designed based on the assumption that there may be two distinct receptor binding sites, per monomer, as with growth hormone. One site would be on the face between helix A and helix C, and the other site would be on the face between helix A and helix D.

---

In The Sequence Listing:

Please replace the Sequence Listing submitted June 29, 2000 with the Sequence Listing attached hereto (**Exhibit D**).

In The Claims:

Please amend claim no. 6 as follows:

C20

---

- 6. The method of claim 5, wherein the receptor binding site comprises approximately amino acid residues 79-95 of the sequence shown in SEQ ID NO:1. -

---

Please amend claim no. 15 as follows:

C21

---

- 15. A method for designing a compound capable of binding to (the) a stem cell factor (SCF) receptor site [of]

---

C-21  
Cont'd

comprising the steps of:

- a) determining a binding site for the SCF receptor on the SCF based on the three-dimensional structure of SCF (SEQ ID NO:1) or an SCF polypeptide or portion/fragment thereof, atomic coordinates computed from X-ray diffraction data of a crystal comprising a polypeptide having an amino acid sequence portion of SCF capable of binding the receptor; and
- b) designing a compound comprising an entity that binds the SCF receptor.

Please amend claim no. 21 as follows:

- C-22 SUB  
D1
- 21. The method of claim 20, wherein the oligopeptide comprises a sequence, wherein functional moiety F<sub>1</sub> corresponds to a segment of amino acid residues from within N-terminal residues 1-10 of SCF (SEQ ID NO:1), functional moiety F<sub>2</sub> corresponds to a segment of amino acid residues from within residues 79-95 of SCF (SEQ ID NO:1), and functional moiety F<sub>3</sub> corresponds to a segment of amino acid residues located within three amino acid residues of amino acid residue 127 of (SEQ ID NO:1), wherein F<sub>1</sub>, F<sub>2</sub>, and F<sub>3</sub> are connected by connecting peptide segments X<sub>n</sub>, X<sub>m</sub>, and X<sub>p</sub>, respectively, wherein n=0-5, m=0-5 and p=3-8 amino acid residues, respectively, and the conjugation moiety F<sub>L</sub> is a cysteine residue.

Please amend claim no. 24 as follows:

- C-23
- 24. The method of claim 15, wherein an appropriate chemical scaffold of connecting segments has been designed to

C23  
Cont'd

comprise (present) functional moieties F<sub>1</sub>, F<sub>2</sub>, and F<sub>3</sub>, which have been selected by combinatorial chemistry for optimal receptor binding from a library of chemical moieties complementary to receptor-binding sites on the surface of SCF (SEQ ID NO:1). --

Please amend claim no. 38 as follows:

C24

--38. The method of claim 37, wherein the isolated SCF analog comprises amino acid residues of native or recombinant SCF1-165 (SEQ ID NO:22) or amino acid residues of a recombinant selenomethionyl SCF1-141 (SEQ ID NO:1). --

Please amend claim no. 39 as follows:

C25

--39. An isolated stem cell factor (SCF) molecule, which is an altered SCF, comprising any portion of amino acids 1-165 of a human SCF polypeptide (SEQ ID NO:1), optionally comprising an N-terminal methionine before amino acid residue 1, wherein the polypeptide has an amino acid sequence portion of SCF capable of binding to the SCF receptor. --

Please amend claim no. 40 as follows:

C26

--40. The altered isolated stem cell factor molecule of claim 39, wherein an alteration is selected from the group consisting of deletion, insertion and substitution of at least one amino acid residue from the naturally occurring amino acid sequence of SCF (SEQ ID NO:1). --

Please amend claim no. 41 as follows:

- c27
- 41. The altered isolated stem cell factor molecule of claim 40, wherein an alteration is a truncated SCF comprising amino acids 1-141 of a human SCF polypeptide (SEQ ID NO:1), optionally comprising an N-terminal methionine before amino acid residue 1. -

Please amend claim no. 42 as follows:

- c28
- 42. The altered isolated stem cell factor molecule of claim 40, wherein the substitution of at least one amino acid residue is selected from the group consisting of SCF(Y26C) (SEQ ID NO:11) disulfide-linked dimer, SCF(D25C) (SEQ ID NO:12), SCF(K62C) (SEQ ID NO:13), SCF(K78N) (SEQ ID NO:14); N81K (SEQ ID NO:15)), SCF(R117A) (SEQ ID NO:16); I118A (SEQ ID NO:17)), SCF(E92A) (SEQ ID NO:18); S95A (SEQ ID NO:19)), and SCF(D124A) (SEQ ID NO:20); K127D (SEQ ID NO:21)). -

Please amend claim no. 47 as follows:

- c29
- 47. The altered isolated stem cell factor molecule of claim 46, wherein the change in said at least one amino acid residue from the naturally occurring amino acid residue(s) is selected from the group consisting of SCF(Y26C) (SEQ ID NO:11) disulfide-linked dimer, SCF(D25C) (SEQ ID NO:12), SCF(K62C) (SEQ ID NO:13), SCF(K78N) (SEQ ID NO:14); N81K (SEQ ID NO:15)), SCF(R117A) (SEQ ID NO:16); I118A (SEQ ID NO:17)), SCF(E92A) (SEQ ID NO:18); S95A (SEQ ID NO:19)), and